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Research Article

Ultrasound Color Doppler of the Middle Cerebral Artery in preterm infants with Intracranial Hemorrhage and Normal Preterm Infants

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Abstract

Introduction: Preterm neonates are at high risk for a wide range of diseases and serious complications, namely intracranial hemorrhage (ICH).

Method: This cross-sectional study included 120 infants (60 preterm infants with intracranial hemorrhage and 60 healthy preterm infants) under 37 weeks old. In the first 3-4 days after birth, color Doppler of the neonatal middle cerebral artery was performed. Then, serial Doppler ultrasound was performed weekly (first four weeks after delivery) for one month and was compared between the two groups.

Results: In this study, among the Doppler parameters in the first week after birth, none of the parameters AT, S/D, PI, RI, and PSV were statistically significant between the two groups of preterm infants with ICH and normal preterm infants (P>0.05).

Conclusions: None of the Doppler parameters AT, S/D, PI, RI, and PSV were statistically significant between the two groups of preterm infants with intracranial hemorrhage and normal preterm infants.

Keywords: Preterm Infants, Intracranial Hemorrhage, Middle Cerebral Artery, Brain Complications.

Introduction

Deliveries before 37 weeks of pregnancy are considered "preterm." Newborns are at higher risk for neonatal medical problems and a wide range of diseases.[1,2] In our country, until 1994, preterm infants accounted for 8% of total births, which has now more than doubled.[3,4] Two-thirds of infant deaths in the United States occur among infants born preterm. Intracranial hemorrhage (ICH) is one of the major neurological disorders in preterm infants at birth. At autopsies of preterm infants who died, 71-56% of them had ICH. 50% of intracranial hemorrhages occur on the first day after birth, and 90% of them happen by the end of one week.[5,6] ICH is associated with dangerous complications such as neuro psychomotor damage and a high risk of cerebral palsy, hydrocephalus, cerebral palsy (CP), seizures, mental retardation, and future death, so early detection and prevention and treatment are essential.[7,8] In ICH, bleeding usually occurs in the subependymal zone (SEZ) and in the germinal matrix (GM), which can push the ependymal cells into the ventricles, leading to complete intraventricular hemorrhage. Apnea crisis, barotraumas, neonatal sepsis, and heart failure are among the risk factors associated with ICH. Some studies have suggested intracranial ischemia as an influential factor in the pathogenesis of ICH. Thus, hypoperfusion in a middle cerebral artery (MCA) and cerebrovascular vessels has led to the destruction of vascular endothelium and increased vascular permeability, followed by vasodilation and increased intravascular ICH. Preterm neonate's arteries are also related to high fragility, which can increase the chances of bleeding .[9-11] In preterm infants, the risk of

tissue hypoperfusion is high due to decreased blood flow to the brain. In these infants, if there is a change in cerebral blood flow, the ability of vascular auto-regulation to adapt to changes in blood pressure is low, tight junction connections between endothelial cells are not well developed, and the vascular basement membrane is not very robust, all of which increase the chances of cerebral hemorrhage and ICH in preterm infants.[12-15] Color Doppler ultrasound is an effective tool for assessing ICH; it is non-invasive, low-priced, and affordable. This device predicts the possibility of both abnormality and pathological findings based on the intensity and speed of blood flow to the cerebral arteries. Numerous hemodynamic factors in various body arteries give different curves that their pulsatility can be low, medium, and high. The curve of each vessel is evaluated based on specific indices, for instance, resistivity index (RI), pulsatility index (PI), and systolic/diastolic (S/D) ratio.[16-19] Color Doppler ultrasound can predict the risk of ICH by measuring the pulsed blood flow inside the cerebral arteries. Decreases in vascular flow rate and intensity indicate hypoxemia and may predict changes in cerebral blood flow and ICH. Also, low PI and RI and high end-diastolic velocity (EDV) in color Doppler indicate low vascular resistance to blood flow and vasodilation, which may predict future ICH.[19] Given the high prevalence of preterm infants in Iran and the need for timely diagnosis and treatment of ICH in these infants, the purpose of this study was to evaluate the color Doppler parameters of MCA artery in terms of ICH diagnosis in preterm infants and its predictive role in brain complications. Doppler coloring of the middle cerebral artery in preterm infants is not routinely performed; however, it is carried out at the request of the appropriate physician.

Methods

This cross-sectional study was conducted for one year, from September 2016 to August 2017, in Alzahra and Taleghani educational and medical centers in Tabriz.

In this study, 120 infants (60 preterm infants with intracranial hemorrhage and 60 healthy preterm infants) under 37 weeks' old were included for one year. This sample size was calculated using the formula $n=2\delta2(Z\alpha+Z\beta)2 / D2$. $Z\alpha$ in this study with a significance of 0.05, equal to 1.96, and $Z\beta$ considering a power of 90% for the survey equal to 1/28. The value of D was calculated according to previous studies, considering the lowest expected difference between the findings. In this study, 120 infants were included in the study; 60 of these infants were in the case group (preterm with intracranial hemorrhage: gestational age between 20 and 37 weeks), and 60 were in the control group (preterm without intracranial hemorrhage). E: We put gestational age above 37 weeks. Gestational age was determined based on ultrasound results and confirmed by a gynecologist. Intracranial hemorrhage was the main criterion for placing patients in the study groups. Also, we matched infants in terms of gender and gestational age to include similar infants in the study. The sampling method in this study was done randomly using a table of incidental numbers from the admissions list.

Inclusion criteria include infants with a birth age of less than 37 weeks and an Apgar score greater than 7; Infants who were utterly healthy according to the requirements of a pediatrician (except ICH) and had the informed and written consent of the infant mother to participate in the interview, study and complete the questionnaire. Exclusion criteria also include unwillingness of one of the baby's parents to continue participating in the survey; Questionnaires with incomplete information; Infants with hypoglycemia; Infants with Apgar less than 7; Infants with asphyxia; Infants with atony; Neonates were cyanotic and infants with other neonatal diseases.

Birth age, sex, birth weight, and other information were recorded in the questionnaire, and in the first 3-4 days after birth, color Doppler of the neonatal MCA was performed. Ultrasound to measure blood flow velocity (BFV), peak systolic velocity (PSV) (S), end-diastolic velocity (EDV) (D) and mean time velocities, pulsatility index, resistive index, S / D in neonatal MCA done. The proximal part of the MCA was examined in the coronal section, and its peripheral branches were discussed in the sagittal section and Sylvain Fisher. Doppler ultrasound (using a Sonosite Micromaxx portable ultrasound machine) was performed serially weekly (first four weeks after delivery) for one month. After collecting and recording data, the first postpartum color Doppler findings were compared between the two groups, and the role of MCA as a primary parameter for ICH was investigated. Cerebral vascular Doppler was executed on the neonatal bedside site from the temporal bone of the head. The infants were kept supine by

relatives or a hospital nurse, and the head was placed in a horizontal position. Based on sonographic findings, the intracranial hemorrhage is graded as follows: Grade I: hemorrhage limited to the germinal matrix (subependymal hemorrhage); Grade II: hemorrhage which has extended into the ventricular system but without dilation of the lateral ventricles; Grade III: hemorrhage extending into the ventricular system with the blood resulting in ventricular dilatation; Grade IV: hemorrhage which extends into the brain tissue.[5]

Data analysis: All data were entered into SPSS software (version 23). The initial display of information was as an average (interquartile range); Chi-square, Mann-Whitney U test, and independent samples t-test were used to compare the data; P-value <0.05 was considered significant.

This study was carried out after being approved by the ethics committee of Tabriz University of Medical Sciences (IR. TBZMED.RECORD.1397.773). The participants signed informed consent and one of their first-degree relatives. The objectives of the research were explained to all participants in simple language. The researchers adhered to all the standards of the Declaration of Helsinki.

Results

Comparison of variables such as Gestational Age (P=0.898), Gender (P=0.559), Birth Weight (P=0.611), Heart rate (P=0.051), Respiratory rate (P=0.300), Body temperature(P=0.360) and SPO2 (P=0.360) between the two groups showed no significant statistical difference(Table 1).

Table 1: Comparison of baseline characters between preterm infants with ICH and normal preterm infants.

Characteristics	Groups(N=120)		
	Case(N=60)	Control(N=60)	P-value
Male/Female *	33/27	35/25	0.559
Gestational Age(week) **	29.2 (25.0 – 30.2)	28.0 (25.3 – 30.0)	0.898
Birth Weight (gram) **	1540.50 (1380.75 – 1650.00)	1610.75 (1480.0 – 1710.30)	0.611
Hear rate ***	151.46±22.6	142.11±21.6	0.051
Respiratory rate ***	56.87±14.2	53.48±14.1	0.300
SPO2 (%) ***	94.80±2.1	94.04±3.2	0.345
Body temperature(^{0}C) ***	36.58±0.6	37.66±0.8	0.360
First minute Apgar ***	7.76±1.3	7.86±1.8	0.411
Fifth minute Apgar ***	9.14±1.5	9.29±0.8	0.503
*Chi square **Mann-Whitney U test *** independent samples t-test.			

In this study, according to Table 2, among the Doppler parameters in the first week after birth, none of the parameters AT, S / D, PI, RI, and PSV were statistically significantly different between the two groups of preterm infants with ICH and normal preterm infants. Also, among the MCA Doppler parameters associated with preterm infants with ICH in four weeks after birth, the AT parameter in the second week for each unit increased in bleeding side AT, healthy side AT significantly increased by 0.436 units; the S / D parameter in the first and second week for each increase in bleeding side S / D, healthy side S / D significantly increased 0.513 (first week) and 0.609 (second week) units, PI parameter in the first week and second, for each unit increase in bleeding side PI, healthy side PI significantly increased 0.470 and 0.671 units, respectively, RI parameter in the first and second week for each unit increase in bleeding side RI, healthy side RI increased 0.536 and 0.527 units, respectively. The PSV parameter in the first, second, and fourth weeks for each increase in the bleeding side PSV and healthy side PSV significantly increased by 0.750 (first week), 0.648 (second week), and 0.821 (fourth week) units (P <0.05).

Table 2: The comparison of Doppler parameters of MCA bleeding side with healthy side in preterm infants with ICH serially up to one month after birth.

Characteristics		First week	Second week	Third week	Forth week
AT	Case	60.0 (35.0 – 350.0)	63.0 (45.0 – 96.0)	63.5 (49.0 – 100.5)	64.5 (50.0 – 89.0)
	Control	55.0 (30.0 – 90.0)	54.0 (35.0 – 85.0)	55.3 (38.5 – 63.11)	55.0 (38.1 – 63.2)
	P-value*	0.346	0.041	0.044	0.059
S/D	Case	3.4 (2.7 – 4.2)	3.9 (2.9 – 4.4)	4.1 (3.5 – 5.0)	4.0 (3.6 – 5.2)
	Control	3.3 (2.8 – 4.3)	3.3 (2.9 – 3.9)	3.6 (3.0 – 4.1)	3.4 (3.0 – 4.2)
	P-value*	0.810	0.059	0.041	0.124
PI	Case	1.3 (1.1 – 1.5)	1.5 (1.1 – 1.8)	1.7 (1.5 – 2.2)	1.5 (1.1 – 2.4)
	Control	1.3 (1.1 – 1.7)	1.1 (1.0 – 1.2)	1.2 (1.0 – 1.05	1.1 (1.0 – 2.0)
	P-value*	0.323	0.045	0.052	0.056
RI	Case	0.7 (0.6 – 0.8)	0.8 (0.6 – 0.9)	0.8 (0.7 – 1.1)	0.8 (0.7 – 1.1)
	Control	0.7 (0.7 – 0.8)	0.7 (0.6 – 0.8)	0.7 (0.6 – 0.8)	0.6 (0.5 – 0.8)
	P-value*	0.997	0.457	0.055	0.112
PSV	Case	38.0 (27.8 – 47.3)	41.0 (35.5 – 49.5)	40.5 (33.5 – 48.1)	42.8 (35.4 – 55.3)
	Control	32.3 (25.6 – 42.5)	35.5 (30.8 – 45.3)	37.0 (33.1 – 41.5)	38.1 (30.0 – 41.0)
	P-value*	0.089	0.047	0.114	0.346

*Mann-Whitney U test

Discussion

This study compared middle cerebral artery Doppler in preterm infants with intracranial hemorrhage and normal preterm infants. The study results show that among the Doppler parameters in the first week after birth, the PI parameter did not show a statistically significant difference between the two groups of preterm infants with ICH and normal preterm infants. In the study by Karlsen et al., Which was a case-control study of 106 pregnancies with intrauterine growth restriction (IUGR), a subgroup (n=26) with postpartum ICH and 212 pregnancies without ICH were matched with gestational age. The findings were that infants with ICH had a higher PI than the control group in the initial study, but this was not significantly assessed in the first 24 hours.[20] The survey by Newman et al., A prospective longitudinal study, included 220 pregnant women whose preterm infants were diagnosed or at risk for gestational age. The results revealed that reducing the ratio of PI in MCA to cerebroplacental ratio (CPR) increases the probability of vascular and cerebral accidents in infants.[21] In the study by Jansen et al., 233 patients were studied with increasing peak blood flow velocity and PI after endarterectomy and the development of unilateral pulsating headache or hypertension. The findings were that peak blood flow velocity and PI increase were significantly higher in patients with intracerebral hemorrhage than in those without intracerebral bleeding. This study concluded that an increase in peak blood flow equal to or greater than 100 or PI equal to or greater than 100 after declamping predicts intracerebral hemorrhage more accurately than headache or hypertension.[22] Bada et al. Examined patients at high risk for intracranial hemorrhage or stroke due to hyperperfusion syndrome. The results showed that significant increases in middle cerebral artery velocity (MCAV) and PI were not able to predict patients at risk for postoperative stroke due to hyperperfusion syndrome (HS) or ICH.[23] In another study by Abdelkader et al. (2017), 123 stroke patients (mean age 14 ± 63 years, 40% women) with anterior circulatory thrombectomy were investigated. Among the participating patients, 18 patients had ICH after the intervention. In this study, PI was not significantly different between the two groups of ICH patients compared to non-ICH patients.[24] Ropacka-Lesiak et al., 2017) showed no statistically significant difference between the two groups of neonates with ICH and without ICH in terms of mean PI in the initial Doppler examination (P-value> 0.05). However, there was a statistically significant difference (P-value <0.001) in terms of mean PI in the follow-up examination.[25]

Based on these findings on the association of middle cerebral artery PI with intracranial hemorrhage, the present study was by the studies of Newman et al., Abdelkader et al., and Ropacka-Lesiak et al. which indicated inadequacy of association between middle cerebral artery PI between patients with ICH and those

without ICH, but conflicted with other studies in that showed a significant association between middle cerebral artery PI and intracranial hemorrhage. There are several possible reasons why this study is inconsistent with these studies, including Differences in the target population and research environment, sample size, and inclusion and exclusion criteria such as disease severity and underlying factors. In this study, among the Doppler parameters in the first week after birth, the RI parameter did not show a statistically significant difference between the two groups of preterm infants with ICH and normal preterm infants. Elhameed et al., 2017, showed no statistically significant difference between the two groups of neonates with ICH and without ICH in terms of mean RI in the initial Doppler examination (P-value> 0.05). However, there was a statistically significant difference (P-value <0.001) in terms of mean RI in the follow-up examination.[22] In the study of Bada et al., The mean value of RI in follow-up examination in preterm infants with ICH was significantly higher than in normal preterm infants.[23] In the study of Abdelkader et al., The RI rate was low in 11 cases out of 19 patients with ICH, which was statistically significantly associated with this disease. [24] Ropacka-Lesiak et al.'s study showed that RI had poor predictive value in predicting fetal abnormal heartbeat at delivery and ICH.[25] In the study of Lobmaier et al., RI MCA less than the 5th percentile had a significant relationship with fetal abnormalities, including ICH (P = 0.049). [26] Based on these findings on the association of middle cerebral artery RI with intracranial hemorrhage, the present study was in harmony with the investigations of Ropacka-Lesiak et al. and Elhameed et al., which indicated a lack of association between middle cerebral artery RI between patients with ICH and those without ICH, but was inconsistent with other studies in that it showed a significant association between middle cerebral artery RI and intracranial hemorrhage. There are several possible reasons why this study is incompatible with such investigations, including Differences in the target population and research environment, sample size, and inclusion and exclusion criteria such as disease severity and underlying factors.

Conclusion

According to the results of this study, none of the Doppler parameters AT, S/D, PI, RI, and PSV were statistically significant differences between the two groups of preterm infants with ICH and normal preterm infants. Among the Doppler parameters in four weeks after birth, most parameters, especially in the first and second weeks, show a statistically significant relationship between the bleeding side and the healthy side in preterm infants with ICH.

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Conflict of Interest Disclosures

The author declares that they have no competing interests.

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Authors' Contributions

All the authors contributed in designing, collecting, analyzing editing the final manuscript.

Ethical Statement

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences before beginning the experiments (research ethics certification code: IR.TBZMED.RECORD.1397.773).

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